Energetic Levels of Metabolic Pathways in Malignant B and T Cells Mini-Review

Aurelian Udristioiu[1], Manole Cojocaru[2]

[1]Clinical Laboratory, Department of Hematology, Emergency County Hospital Targu Jiu & UCB University, Romania

[2]Titu Maiorescu University, Faculty of Medicine, Physiology Department, Bucharest, Romania

[1]aurelianu2007@yahoo.com; [2]mancojocaru@yahoo.com

Abstract

Recent evidences suggested that metabolites themselves can be oncogenic by altering cell signaling and blocking cellular differentiation. The advances in cancer metabolism research over the last decade, have enhanced our understanding regarding the aerobic glycolysis and other metabolic alterations that are associated with cell growth and proliferation.

The blocked apoptosis in malignant diseases, which may be due to high ATP concentration, originating from anaerobic metabolism. The difference of energy between anaerobic ATP into B and T lymphocytes in peripheral blood samples from hematopoietic malignant diseases measured by bioluminescence, was 2.68 μM ATPthat appears as an energetic transfer between normal T and B cells, initial with normal bio-energetic values. This energetic level could initiate the process of carcinogenesis by the supression of anti-oncogene proteins from its normal activity.

The anabolic metabolism in B and T cells from malignant diseases is under a complex regulatory control directed of membrane receptors, associated with growth factors signals of transduction in transformed cells.

Keywords

Adenosine-triphosphate; Chronic Lymphocytic Leukemia; Tumor Suppressor Gene P53; Tumor Necrosis Factor; Zeta-chaine-associated Protein Kinase 70

Introduction

Chronic lymphocytic leukemia (CLL) is associated with abnormalities of the B-Cell Receptor (BCR) signaling, including low responsiveness to antigenic stimulation and constitutive phosphorylation of several components of the signaling pathway. Surface receptors, (e.g., B or T cell antigen receptors), in part, are linked by the growth factors to signal transduction/metabolic pathways in the cell cycle.

The International Workshop on CLL (IWCLL) 2008 updated the criteria for diagnosing and initiating treatment of CLL (Hallek H. et al, 2008). Activated B lymphocytes were defined as CD19 + cells, CD20, CD21, and CD23 and or CD 38 surface markers. The phenotype of CLL cells, characterized by the presence of several B-cell markers such as CD19, CD20, and CD23 along with CD5, an antigen normally found on T cells, was used for an initial diagnosis of CCL.

Among these receptors, CD20 receptor is highly expressed on malignance B-cell precursors, including diffuse large B-cell, lymphoma (DLBCL), non-Hodgkin lymphoma and CLL (Wojciechowski W. et al, 2005). Diffuse large B-cell lymphoma (DLBCL) is considered to be the most common type of lymphoma in adults, accounting for 30% to 40% cases of non-Hodgkin lymphoma.

Also, the CD40 receptor, a tumor necrosis factor receptor super-family, member 5 (TNFRSF5 sequence gene), is expressed throughout B-cell development. Ligation of B-cell CD40 by its ligand CD154 (TNFSF5) expressed on activated T cells, has an important role in T cell–mediated B lymphocyte activation (Gricks SC. et al, 2004, Boulassel RM. et al, 2012).

A high level of CD40 expression was detected on a wide range of malignant cells including B- cell neoplasms, bladder cells, and carcinoma cell types, among others. It has been reported that in Hodgkin's lymphoma, hairy cell leukemia, chronic lymphocytic leukemia, and follicular lymphomas, CD40 activation contributed to tumor survival and resistance to chemotherapy. [Figure 1].

CD40L induction showed a significantly higher rate of apoptotic cells. Combining CD40L and B cell receptors (BCR) stimulation revealed a significant decrease of TOSO expression, also known as Fas-inhibitory molecule 3 (FAIM3), compared with native CLL cells (Choi CS. et al, 2010).

TOSO was described as a novel marker overexpressed in CLL cells and as a new anti-apoptotic factor in CLL

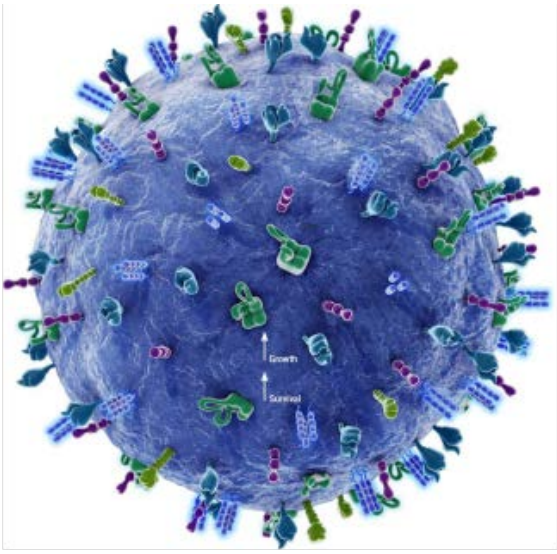

Figure 1 Over-expression of cellular receptors on surface malignant cell B cells express a variety of specific surface antigens that can theoretically act as targets for chimeric antigen receptors (CAR) which kill leukemic cells

pathogenesis, triggered by BCR signaling and further regulated by stroma interaction via the CD40 molecule (Pallasch PK. Et al, 2008).

In last few years, it was show that the anti-apoptotic factor TOSO is associated with progressive disease and enhanced in the proliferative CD38-CLL subset (Hitoshi Y. et al, 1998, Pallasch PC. et al, 2008).

Also it was demonstrated that CD150 receptor could trigger PI3K)/Akt (phosphatidylinositol 3 kinase mediated Akt-protein kinase B) signaling pathway) in malignant B cells (Di Cosimo S. et al, 2007, Boulassel RM. et al 2012.).

Body of review in energetic metabolic pathways in malignant B cells

The use of Ca^{2+} as a second messenger rests on the maintenance of a low cytosolic Ca^{2+} concentration, through the energy-consuming pumping activity of Ca^{2+} ATP-ase located in endoplasmic reticulum (ER)/ sarcoplasmic reticulum (SR) (SERCA) or on plasma membrane (PMCA). Studies demonstrated that Ca^{2+} ions increasing in the cytosol, (and hence in mitochondria) are able to activate mitochondrial ATP synthesis. This effect lasts longer than the Ca^{2+} signal itself, highlighting a form of cellular metabolic memory (Mbaya E. et al, 2010).

The plasma membrane and its constituent phosphor-inositides form the basis of PI3-K signaling pathway that is crucial for cell proliferation and survival of cells. Akt (protein kinase B) is an essential downstream effector in PI3-K signaling that regulates cell proliferation and survival inhibiting apoptosis (Yasui T. et al, 2012).

In normal cells, the glucose carbon flow is directed into a de novo lipogenic pathway that is regulated, in part, via phosphoinositide-3 kinase (PI-3K)-dependent activation of ATP citrate lyase (ACL), a key rate-limiting, enzyme in de novo lipogenesis. ACL is a cytosolic enzyme that catalyzes the generation of acetyl CoA from citrate. The inhibition of ACL results in a loss of B-cell growth and cell viability (.Zaidi N. et al, 2012), [Figure 2].

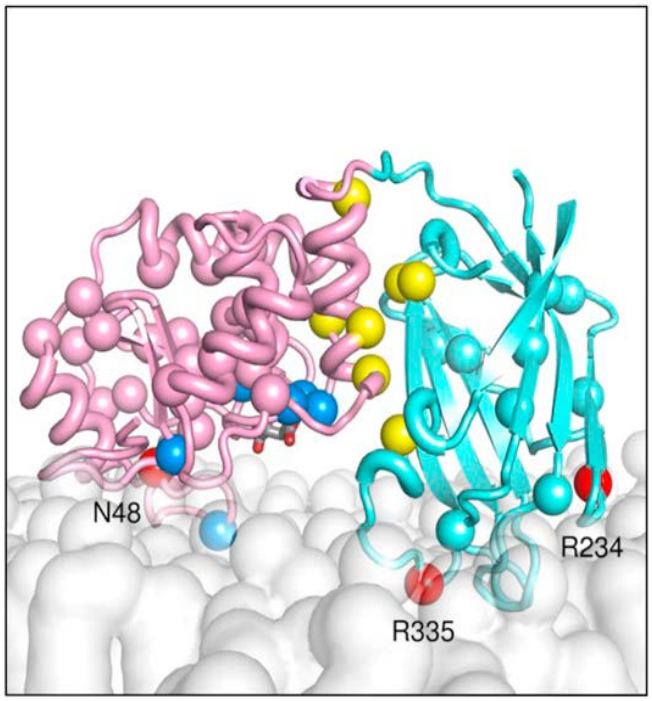

Figure 2 Locations of membrane-interacting in clinically important mutations

ACLY is up-regulated or activated in several types of cancers, and its inhibition is known to induce proliferation arrest in cancer cells both in vitro and in vivo. The previous studies showed that BCR-mediated signaling is regulated in part by the amount of membrane cholesterol. It was observed that statins (Lovostatin), the pharmacological inhibitors of cholesterol synthesis, induce apoptosis of CLL cells in vitro and in vivo. Also the ectopic expression of CD5 in a B-cell line stimulates the transcription of genes involved in the synthesis of cholesterol (Tomowiak C. et al, 2012).

Most non-proliferating, differentiated cells depend on the efficiency of ATP production through oxidative phosphorylation to maintain their integrity. As a result, such cells metabolize glucose to pyruvate through glycolysis, and then completely oxidize most of this pyruvate to CO^2 through the tricarboxylic acid (TCA)

cycle of the mitochondria, where oxygen is the final acceptor in an electron transport chain that generates an electrochemical gradient facilitating ATP production. The pyruvate dehydrogenase (PDH) complex that converts glucose-derived pyruvate into acetyl-CoA is solely mitochondrial. Mitochondrial acetyl-CoA then cannot be directly exported to the cytoplasm but instead it must first condense with oxaloacetate to form citrate through the activity of another exclusively mitochondrial enzyme, citrate synthase (Ward SP. et al, 2012).

Cytosolic NADPH might be limited for cell proliferation because its level is critical for providing reducing equivalents for fatty acid and cholesterol biosynthesis, as well as for modulating oxidative stress.

It is known from experimental studies that metformin, a potent anti-hyperglycemic agent induces apoptosis of CLL cells (Viollet B. et al, 2012). The main effect of this drug from the biguanide family is to acutely decrease hepatic glucose production, mostly through a mild and transient inhibition of the mitochondrial respiratory-chain complex. In addition, the result decreases liver energy, activates the AMP-activated protein kinase (AMPK), a cellular metabolic sensor. Activated AMPK switches cells from an anabolic to a catabolic state, shutting down the ATP-consuming synthetic pathways and restoring energy balance.

It has been suggested that metformin could inhibit the growth of cancer cells by decreasing cellular energy status and force a metabolic conversion that cancer cells are unable to execute. A recent study revealed that AMPK activation promotes the survival of cells metabolically impaired by glucose limitation in part through p53 activation (Buzzai M. et al, 2007).

Also, the tumor-specific mutations in IDH1 and IDH2 have resulted in loss of their normal enzymatic activity of interconvert isocitrate at ketoglutarate acid expressed in hematopoietc malignant cells (Patrick S. et al, 2012).

In earlier studies, it was highlighted that epigenetic abnormalities may have the potential to increase the risk of tumor-genesis (Podlaha O. et al, 2010). Mechanisms of chromatin remodeling include dynamic interplay among ATP-dependent complexes, covalent histone modifications, utilization of histone variants and DNA methylation. Chromosomal rearrangements studies in chronic lymphocytic leukemia led to the hypothesis that cancer cells may undergo catastrophic events, whereas in the genome a large number of rearrangements are required within a single breakage–fusion events (Stephens PJ, et al, 2011), Wang GG. Et al, 2007, De S. et al, 2011), [Figure 3].

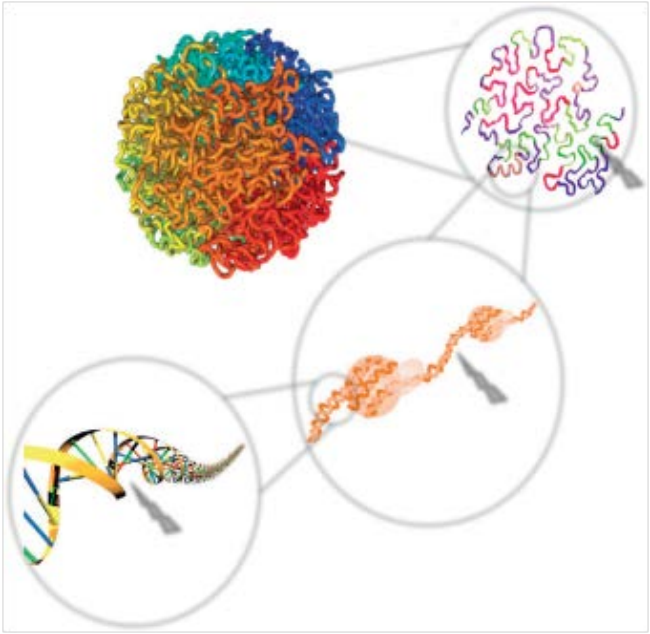

Figure 3 Genetic and epigenetic determinants of cancer genome evolution

The human genome is organized into highly complex structures with multiple levels of organization. The highest level comprises chromosome packaging into the cell nucleus (a). DNA strands in close spatial proximity are more likely to interact during replication and transcription, leading to chromosomal rearrangements and gene fusions (b). Aberrant methylation and acetylation of histone tails can result in gene expression and splicing variation (c). DNA sequence alterations may modulate gene expression and change protein amino acid composition (d). Aberrations at all of these levels may influence the mutational landscape of cancer genomes.

In previous studies, it was shown that activation of Akt is sufficient to increase glucose utilization in B cells (Lunt YS. Et al, 2011), but in the recent studies the important role of Akt and mTOR (mammalian target of rapamycin) signaling is surprising given in regulating nutrient uptake in hematopoietic cells.

The activated mTOR has also been implicated in the development of endoplasmic reticulum (ER) oxidative stress (Jones GR. Et al, 2009), [Figure 4].

The PI3K/AKT/mTOR pathway, commonly activated in human cancers, is a key regulator of survival and apoptosis, cell cycle and growth, protein synthesis, and glucose metabolism (Craig N. et al, 2013). AKT,

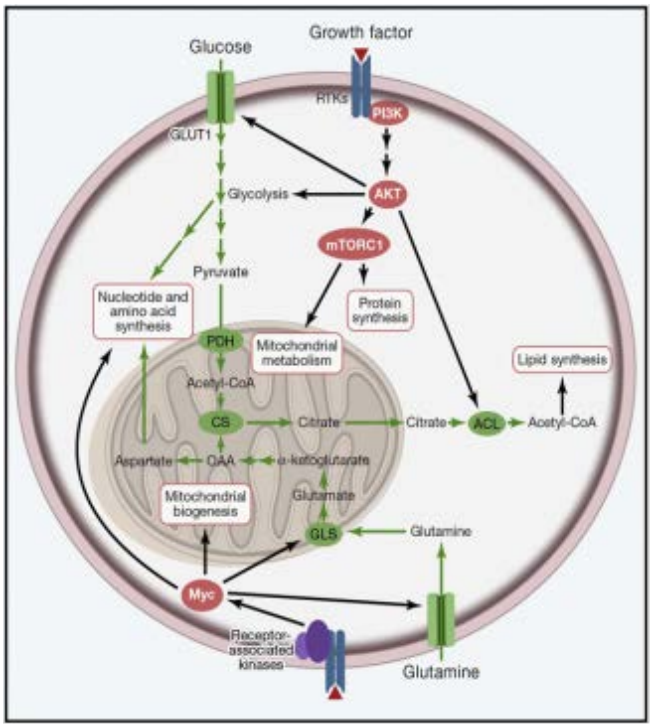

Figure 4 Alterations of classic oncogenes in directly reprograming cells

which lies downstream of PI3K, stimulates glycolysis by increasing the expression and membrane translocation of glucose transporters, and by phosphorylating key glycolytic enzymes, such as hexokinase.

Biosynthesis of PI3K/Akt signaling, downstream of receptor tyrosine kinase (RTK) activation, increases glucose uptake through the transporter GLUT1, and increases flux through glycolysis. Branches of glycolytic metabolism contribute to nucleotide and amino acid synthesis. Akt also activates ACL, promoting the conversion of mitochondria-derived citrate to acetyl-CoA for lipid synthesis. In addition, proto-oncogene Myc promotes nucleotide and amino acid synthesis, both through direct transcriptional regulation and through increasing the synthesis of mitochondrial metabolite precursors.

Interpretation of ATP values in normal and malignant cells

Proliferative metabolism is heavily dependent on the reprogramming of mitochondria to serve a synthetic rather than a degradative role. The metabolic changes, associated with proliferating cells, do not simply occur passively in response to damaged mitochondria or changes in ATP levels.

In the healthy male and female subjects, the mean blocked apoptosis in malignant diseases may be due to the high concentration of ATP from anaerobic metabolism. Energy difference between anaerobic ATP B and T lymphocytes in peripheral blood samples from hematopoietic malignancies measured by bioluminescence was 2.68 uM ATP that appears as an energy transfer between normal cells and T cells normal B normal initial energy values. The energy level can initiate the process of carcinogenesis by suppressing the activity of anti-oncogene proteins, (Udistioiu A. and Co, 2010).

TABLE 1 THE CONCENTRATIONS OF μM ATP IN MALIGNANT CELLS CONTENTED IN 10^6 lymphocytes / ml, FROM PERIPHERAL BLOOD.

Normal conc. ATP in T cells μM	Normal conc. ATP in B cells μM	Conc. ATP in T cells, malignant diseases	Conc. ATP B cells in malignant disease	Conc. ATP in B cells from CLL	Conc. ATP in T cells from CLL
$\bar{x}$= 1.39	$\bar{x}$=0.35	$\bar{x}$== 3.06	$\bar{x}$= 0.17	$\bar{x}$=4.33	$\bar{x}$= 0.09
SD=0.41	SD=0.42	SD = 0.46	SD = 0.45	SD =1.5	SD =1.7

From patients with different malignant diseases in advance with metastasis (lung cancer, liver cancer, bone cancer), the concentration of ATP in 1 x 106 reactive T lymphocytes/ml had a mean value of 3.06 μM ATP and the mean concentration of ATP in 1 x 106 B lymphocytes/ml was 0.17 μM ATP [SD= 0.45, p = 0.05]. The mean concentration of ATP in 1 x 106 B cells from CLL was 4.33 μM ATP but only 0.09 μM ATP [SD= 1.5, p< 0.05] in T lymphocytes from these patients, [Table 1].

A strong correlation was observed between ATP concentration in T lymphocytes from patients with malignant diseases and ATP concentration in B lymphocytes from samples of patients with CLL (r= 0.99). Recent work has revisited how proliferating cells maintain glycolytic flux by either minimizing ATP production or enhancing ATP consumption.

Another study has suggested that elevated concentration of adenosine-triphosphate (ATP) in malignant B cells lymphocytes from CLL impaired P53 gene to induce apoptosis cells.

Effects of activated proto-oncogene in initiating carcinogenetic process

Mouse model links defective pre-BCR signaling to oncogenic c-Myc activation and disruption of the p19Arf-Mdm2-p53 tumor suppressor pathway which also play an essential role in the pre-B cell transformation process, (Van BT. et al 2010). Elevated c-Myc protein is correlated with increased mutant p53 mRNA in Burkitt's lymphoma cells. If c-Myc can activate the human p53 gene, then one prediction would be that tumor cells expressing elevated c-Myc may express elevated mutant p53 mRNA. This type of

correlation has been reported in the literature previously (Roy B. et al, 1994, Vassilev LT. et al, 2004)

It was demonstrated that the human p53 promoter is trans-activated by high c-Myc expression and repressed by high max-expression. In examining the relative levels of c-Myc and p53 in human Burkitt's lymphomas and other B-lymphoid lines, hypotesis was made that there is a correlation between the levels of c-Myc protein and p53 mRNA expression. In particular, cells which express very low levels of c-Myc protein also express low levels of p53mRNA, while cells that express high levels of c-Myc tend to express high levels of p53 mRNA, (Starczynowski DT. et al, 2011).

Micro RNAs (miRNAs) are small non-protein-coding RNAs that regulate genes expression by inhibiting the translation or catalyzing the degradation of target mRNAs. Since the first miRNA, lin-4, was identified in 1993, miRNAs have been shown to play critical roles in the regulation of many biological processes including cell differentiation, proliferation, and apoptosis, with significant influences on normal and malignant hematopoiesis, (Chung S. et al, 2011).

The miRNAs are endogenous small non-coding RNAs, in 18 to 25 in nanometers length, which regulate gene expression. The miRNA-mediated regulation of gene expression may take place either through mRNA degradation or inhibition of translation. miRNAs bind to the 30-untranslated region. (30-UTR)) of the target mRNA has imperfect base pairing and thus being able to regulate a large number of genes simultaneously, (Stephens P. et al, 2011, Lunt YS. et al, 2011).

Therefore, miRNAs act as master gene regulators, similar to transcription factors, and the two may cooperate and ultimately determine gene expression patterns in the cell (Jones GR. et al, 2009, Hatziapostolou M. et al, 2013).

This is an intriguing observation, since miR-34a has been identified as a P53 target with pro-apoptotic functions. Thus, it is interesting to speculate that *miR-34a* may regulate p53 activity, thereby contributing to leukemic stem cells (LSC) development, quiescence, or resistance to therapy.

Various mechanisms of apoptosis resistance in CLL have been described, such as over-expression of bcl2 mediated by depletion of inhibitory miR-15 and miR-16.3. Accumulating evidences indicated that the signal transduction-dependent, changes in both glucose energy metabolism and de novo transcription of the D-type cyclin-cdk4/6 pathway are necessary for quiescent B-lymphocytes to enter G1-phase of the cell cycle and grow (Shapiro IG. et al, 2006).

Cyclin-dependent kinases (cdks) are critical regulators of cell cycle progression and RNA transcription. A variety of genetic and epigenetic events cause universal over-activity of the cell cycle cdks in human cancer, and their inhibition can lead to both cell cycle arrest and apoptosis. The frequency of cyclin D–cdk4/6–INK4 pathway alterations suggests that acceleration of G_1 progression provides a proliferative and, perhaps survival advantage to cancer cells.

Constitutive activation of protein kinases, mainly by phosphorylation, has been linkated as contribution to malignant phenotypes in a number of human cancers. AKT is a serine threonine kinase that gets activated on growth factor and cytokine stimulation, Uddin S. et al, 2006).

Autophagy is a cellular process that maintains the homeostasis of the normal cell. The interdependency of metabolism and cellular mechanisms such as autophagy are becoming more evident and important (Banerji V. et al, 2012). The initial signal to form auto-phagosomes is by the class III phosphatidyl-inositol (PI) 3 kinase complex consisting of sequence genes, Beclin1/Atg6, p150hVSp35, and class III PI3K (Vps34). This process is negatively regulated by binding of Bcl-2 family members such as Bcl-x_L to Beclin1 preventing Beclin1 binding to the PI3K-III complex and thereby reducing autophagy.

Body of review in energetic metabolic pathways in malignant T cells

Antigen stimulation of T cell receptor (TCR) signaling to nuclear factor (NF)-B is required for T cell proliferation and differentiation of effector cells. The TCR-to-NF-B pathway is generally viewed as a linear sequence of events in which TCR engagement triggers a cytoplasmic cascade of protein-protein interactions and post-translational modifications, ultimately culminating in the nuclear translocation of NF-B.

Activation of effect or T cells leads to increased glucose uptake, glycolysis, and lipid synthesis to support growth and proliferation (Gerriets AV. Et al, 2012).

Activated T cells were identified with CD7, CD5, CD3, CD2, CD4, CD8 and CD45RO. Simultaneously, expression of CD95 and its ligand causes apoptotic cells death by paracrine or autocrine mechanism and during inflammation, IL1-β and interferon-1α induce

massive CD up-regulation [. Michalek, RD. et al, 2011].

Indeed, direct manipulation of glucose metabolism in vivo has been shown to modulate inflammatory disease. Over-expression of the glucose transporter Glut1 leads to increased glucose uptake and glycolysis, and transgenic expression of Glut1specifically in T cells leads to increased T cell proliferation, survival and cytokine production.

Glut1 is expressed at a low level in naıve T cells and rapidly induced by Myc following T cell receptor (TCR) activation. Glut1 trafficking is also highly regulated with Glut1 protein remaining in intracellular vesicles until T cell activation, (Wang, R, et al 2011).

CD28 co-stimulation to further activates the PI3K/Akt/mTOR pathway in particular, and provides a signal for Glut1 expression and cell surface localization (28). Mechanisms that control T cell metabolic reprogramming are now coming to light, and many of the same oncogenes important in cancer metabolism are also crucial to drive T cell metabolic transformations, most notably Myc, hypoxia inducible factor (HIF)1a, estrogen-related receptor (ERR) a, and the mTOR pathway.

The proto-oncogenic transcription factor Myc is known to promote transcription of genes for the cell cycle as well as aerobic glycolysis and glutamine metabolism. Recently, Myc has been shown to play an essential role in inducing the expression of glycolytic and glutamine metabolism genes in the initial hours of T cell activation. In a similar fashion, the transcription factor HIF1a can up-regulate glycolytic genes to allow cancer cells to survive under hypoxic conditions, (Semenza G.L, Shi L.Z. et al, 2011).

The protein ZAP70, Zeta-chain-associated protein kinase 70 is a member of the protein-tyrosine kinase family. ZAP70 is normally expressed in T cells and natural killer cells, and has a critical role in the initiation of T-cell signaling. ZAP70 in B cells is used as a prognostic marker in identifying different forms of chronic lymphocytic leukemia (CLL). More recently, CD73 has been investigated as a potential diagnostic marker in T leukemia. CD73 has been found to be overexpressed and in CLL-T, on a subset of chronic lymphocytic leukemia clones in 30% of patients (n=299), marking a subset phenotypically associated with more aggressive clinical behavior and proliferation. (Beavis AP. et al, 2012).

Although CD73 is required for the conversion of AMP into adenosine in physiological conditions, loss of function mutations in the CD73 gene leads to an increase in the expression of tissue-non-specific alkaline phosphatases. Thus, at least to a certain extent, alkaline phosphatases have the capacity to compensate for lack of CD73 function, which may be important in maintaining homeostasis under such conditions (Livolsi A. et al, 2001).

It can be concluded that the most important cell-regulatory mechanisms of energetic metabolic pathways, in mammalian T cells and B cells are: death receptors, caspases, mitochondria, the Bcl-2 family proto-oncogene, tumor suppressor gene TP53, TNF, and nuclear translocation factor, NF-Kb and recently Micro RNAs (miRNAs) which are small non-coding RNAs that act at the posttranscriptional level to regulate protein expression (Yurchenko M. et al, 2011).

Conclusions

High concentrations of anaerobic ATP could impair the apoptosis from CLL. Further studies are necessary to detect patients with high concentrations of ATP the mutations, translocations or deletions of the p53 gene, using molecular complex technologies, in the discovery of mechanisms in the carcinogenesis process.

REFERENCE

Banerji V, Gibson BS. Targeting Metabolism and Autophagy in the Context of Haematologic Malignancies. IJ Cell Biology 1 (2012): 2-11.

Beavis AP, Stagg J, Darcy KP Smyth J.M. CD73: a potent suppressor of anti-tumor immune responses. Trends in Immunology 1 (2012):1471-1478.

Boulassel RM, Gala A. Immunotherapy for B-Cell Neoplasms using T Cells expressing. Chimeric Antigen Receptors Sultan Qaboos Univ Med J 12(3), (2012): 273–285.

Buzzai M, Jones RG, Amaravadi RK, Lum JJ, et al. Systemic treatment with the antidiabetic drug metformin selectively impairs p53-deficient tumor cell growth. Cancer Res 67(2007): 6745–6752.

Craig N. Lumb and Mark S.P. Sansom. Defining the Membrane-Associated State of the PTEN Tumor Suppressor Protein. Biophys J 5; 104(3), (2013): 613–621.

Chung S, Hu W, Park C. The role of microRNAs in hematopoietic stem cell and leukemic stem cell function. Therapeutic Advances in Hematology 5(2), (2011): 317-

334.

Choi CS, Narayanan S,Krzewski K,Borrego K et al. Expression and regulation of Toso, a new Fc receptor for IgM, during B cell development. Int. Immunol 22 (3), (2010): 149-156.

D Glick, S. Barth, and K. F. Autophagy: cellular and molecular mechanisms. Journal of Pathology 221 (1), (2010): 3–12.

Di Cosimo S, Scaltriti M, Val D, et al. The PI3-K/AKT/mTOR pathway as a target for breast cancer therapy Journal of Clinical Oncology 25 (18S), (2007): 3511.

De S, Michor F. DNA secondary structures and epigenetic determinants of cancer genome evolution. Nat Struct Mol Biol 3;18 (8), (2011): 950-955).

Frauwirth K.A, Riley J.L, Harris M.H, Parry R.V, Rathmell J.C. et al. The CD28 signaling pathway regulates glucose metabolism. Immunity 16 (2002): 769–777.

Gerriets AV, Rathmell C.J.2012.Metabolic pathways in T cell fate and Function. Trends in Immunology; 33 (4), (2012): 168-173.

Gricks SC, Zahrieh D, Zauls JA, Gorgun G. Differential regulation of gene expression following CD40 activation of leukemic compared to healthy B cells. Blood 104 (2004): 4002-4009.

Hallek H, Cheson DB, Catovsky D, Cappio CF. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 Guidelines. Blood 111 (12), (2008): 5446-5456.

Hatziapostolou M, PolytarchouC, Iliopoulos D. Micro miRNAs link metabolic reprogramming to oncogenesis. Trends in Endocrinology and Metabolism 24(4), (2013): 114-116.

Hitoshi Y, Lorens J, Kitada SI, et al. Toso, a cell surface, specific regulator of Fas-induced apoptosis in T cells. Immunity 8(1998): 461-471.

Jones GR, Thompson BC. Tumor suppressors and cell metabolism: a recipe for cancer growth Genes & Dev; 23(2009): 537-548.

Livolsi A, Busuttil V, Imbert V, Abraham RT, Peyron JF. Tyrosine phosphorylation-dependent activation of NF-κB. Requirement for p56 LCK and ZAP70 protein tyrosine kinases. Eur. J. Biochem 5 (2001): 1508–1515.

Lunt YS, Heiden VGM. Aerobic Glycolysis: Meeting the Metabolic Requirements of Cell Proliferation. Annual Review of Cell and Developmental Biology 27(2011): 441-464.

Mbaya E; Oulès B; Caspersen C; Tacine R et al. Controlling metabolism and cell death: at the heart of mitochondrial calcium signaling. Biochimica et Biophysica

Acta 1977 (6-7), (2010): 945-51.

Michalek RD et al.Cutting edge: distinct glycolytic and lipid oxidative metabolic programs are essential for effector and regulatory CD4+ T cell subsets. J. Immunol 1869 (2011): 3299–3303.

Pallasch PC, Schulz A, Kutsch N, Schwamb J. Over-expression of TOSO in CLL is triggered by B-cell receptor signaling and associated with progressive disease, Blood 112 (2008): 4213-4219.

Patrick S. Ward, Craig B. Thompson1. Metabolic Reprogramming: A Cancer Hallmark Even Warburg Did Not Anticipate Cancer Cell 21 (2012): 297 308.

Podlaha O, Riester M, De S, Michor F. Evolution of the cancer genome. Trends Genet 28(4), (2012): 155-163.

Roy B, Beamon J, Balint E, Reisman D. Transactivation of the Human p53 Tumor Suppressor Gene by c-Myc/Max Contributes to Elevated Mutant p53 Expression in Some Tumors. Molecular and Cellular Biology 14 (12), (1994): 7805-7815.

Semenza G.L. Regulation of oxygen homeostasis by hypoxia inducible factor 1. Physiology Bethesda 24(: 2009); 97–106.

Shapiro IG. Cyclin-Dependent Kinase Pathways As Targets for Cancer Treatment, JCO 24(11), (2006): 1770-1783.

Shi LZ, Wang R, Huang G, Vogel P et al. HIF1alpha-dependent glycolytic pathway orchestrates a metabolic checkpoint for the differentiation of TH17 and Treg cells. J. Exp. Med 208 (2011): 1367–1376.

Starczynowski DT, Morin R, McPherson A, Lam J. Genome-wide identification of human microRNAs located in leukemia-associated genomic alterations Blood 117 (2),(2011): 595-607.

Stephens PJ, Greenman C.D, Fu B, Yang F et al. Massive genomic rearrangement acquired in a single catastrophic event during cancer development. Cell 144 (1), (2011):

27–40.

Tomowiak C, Kennel A, Gary-Gouy, Hadife N. High Membrane Cholesterol in CLL B-Cells and Differential Expression of Cholesterol Synthesis Genes in IG GENE Unmutated vs Mutated Cells. British Journal of Medicine & Medical Research 2(3), (2012): 313-326.

Uddin S, Hussain RA, Siraj KA, Manogaran SP. B-cell lymphoma survival Role of phosphatidylinositol 3¢-kinase/AKT pathway in diffuse large. Blood 108(2006): 4178-4186.

Udristioiu A, Florescu C, Popescu M.A. High Concentration of anaerobic ATP implicated in aborted apoptosis from CLL. LabMedicine 41(4), (2010) ; 203-208.

Vassilev LT, Vu TB, Graves B, Carvajal D, et al. In vivo activation of the p53 pathway by small molecule antagonists of MDM2. Sci 303(5659), (2004): 844-848

Van BT, Marjolein JW, Petra J, Hamburg PJ. Malignant transformation of Slp65-deficient pre-B cells involves disruption of the Arf-Mdm2-p53 tumor suppressor pathway Blood 115, (2010):1385-1393.

Viollet B, Guigas B, Sanz Garcia N, Leclerc J. Cellular and molecular mechanisms of metformin: an overview. Clin Sci (Lond) 122(6), (2012): 253–270.

Wang R., Dillon C.P, Shi L.Z, Milasta S et al. The transcription factor Myc controls metabolic reprogramming upon T lymphocyte activation. Immunity 35(2011): 871–882.

Ward SP, Thompson BC. Metabolic Reprogramming: A Cancer Hallmark Even Warburg Did Not Anticipate. Cancer Cel 21(3), (2012) : 297–308.

Wojciechowski W, Li H, Marshall S et al. Enhanced expression of CD20 in human tumor B cells is controlled through ERK-dependent mechanisms. J Immunol 2005; 174:7859-7868.

Zaidi N, Swinnen JV, Smans K. ATP-citrate lyase: a key player in cancer metabolism Cancer Res 15 (2012): 3709-3714.

Yasui T, Yada SK, Nishimura T, Morit K. Protein kinase N1, a cell inhibitor of Akt kinase, has a central role in quality control of germinal center formation. PNAS 1(2012): 1-6.

Yurchenko M, Shlapatska LM, Romanets OL, Ganshevskiy D et all. CD150-mediated Akt signalling pathway in normal and malignant B cells Exp Oncol 33(1), (2011):9-18.

Roy B, Beamon J, Balint E, Reisman D. Transactivation of the Human p53 Tumor Suppressor Gene by c-Myc/Max Contributes to Elevated Mutant p53 Expression in Some Tumors. Molecular and Cellular Biology 14 (12), (1994): 7805-7815. Semenza G.L. Regulation of oxygen homeostasis by hypoxia inducible factor 1. Physiology Bethesda 24(: 2009); 97–106. Shapiro IG. Cyclin-Dependent Kinase Pathways As Targets for Cancer Treatment, JCO 24(11), (2006): 1770-1783. Shi LZ, Wang R, Huang G, Vogel P et al. HIF1alpha-dependent glycolytic pathway orchestrates a metabolic checkpoint for the differentiation of TH17 and Treg cells. J. Exp. Med 208 (2011): 1367–1376. Starczynowski DT, Morin R, McPherson A, Lam J. Genome-wide identification of human microRNAs located in leukemia-associated genomic alterations Blood 117 (2),(2011): 595-607. Stephens PJ, Greenman C.D, Fu B, Yang F et al. Massive genomic rearrangement acquired in a single catastrophic event during cancer development. Cell 144 (1), (2011): 27–40. Tomowiak C, Kennel A, Gary-Gouy, Hadife N. High Membrane Cholesterol in CLL B-Cells and Differential Expression of Cholesterol Synthesis Genes in IG GENE Unmutated vs Mutated Cells. British Journal of Medicine & Medical Research 2(3), (2012): 313-326. Uddin S, Hussain RA, Siraj KA, Manogaran SP. B-cell lymphoma survival Role of phosphatidylinositol 3¢-kinase/AKT pathway in diffuse large. Blood 108(2006): 4178-4186. Udristioiu A, Florescu C, Popescu M.A. High Concentration of anaerobic ATP implicated in aborted apoptosis from CLL. LabMedicine 41(4), (2010) ; 203-208.

Vassilev LT, Vu TB, Graves B, Carvajal D, et al. In vivo activation of the p53 pathway by small molecule antagonists of MDM2. Sci 303(5659), (2004): 844-848 Van BT, Marjolein JW, Petra J, Hamburg PJ. Malignant transformation of Slp65-deficient pre-B cells involves disruption of the Arf-Mdm2-p53 tumor suppressor pathway Blood 115, (2010):1385-1393. Viollet B, Guigas B, Sanz Garcia N, Leclerc J. Cellular and molecular mechanisms of metformin: an overview. Clin Sci (Lond) 122(6), (2012): 253–270. Wang R., Dillon C.P, Shi L.Z, Milasta S et al. The transcription factor Myc controls metabolic reprogramming upon T lymphocyte activation. Immunity 35(2011): 871–882. Ward SP, Thompson BC. Metabolic Reprogramming: A Cancer Hallmark Even Warburg Did Not Anticipate. Cancer Cel 21(3), (2012) : 297–308. Wojciechowski W, Li H, Marshall S et al. Enhanced expression of CD20 in human tumor B cells is controlled through ERK-dependent mechanisms. J Immunol 2005; 174:7859-7868. Zaidi N, Swinnen JV, Smans K. ATP-citrate lyase: a key player in cancer metabolism Cancer Res 15 (2012): 3709-3714. Yasui T, Yada SK, Nishimura T, Morit K. Protein kinase N1, a cell inhibitor of Akt kinase, has a central role in quality control of germinal center formation. PNAS 1(2012): 1-6.

Yurchenko M, Shlapatska LM, Romanets OL, Ganshevskiy D et all. CD150-mediated Akt signalling pathway in normal and malignant B cells Exp Oncol 33(1), (2011):9-18.